

Relationship between composition and organizational levels of nanostructured systems formed by Oleth 10 and PPG-5-Ceteth-20 for potential drug delivery

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In this paper, nanostructured systems were developed, with the aid of ternary phase diagrams, from two surfactants, of differing degrees of lipophilicity (PPG-5-Ceteth-20 and the Oleth 10) and two oil phases (oleic acid and isopropyl myristate). It was observed that there were differences between the four resulting phase diagrams in the physical properties of the systems they represent. Thus, due to the capacity of Oleth 10 (as surfactant) and oleic acid (as the oil phase) to reduce interfacial tension, large regions of translucent systems were seen on the diagrams produced by them. By polarized light microscopy, it was possible to identify the isotropic and anisotropic properties of these systems, which were confirmed by small-angle X-ray scattering (SAXS) analysis. Furthermore, it was found that increasing the proportion of water in the formulations led to more highly organized structures, resulting in narrower and well defined SAXS peaks.

Uniterms: Ternary phase diagrams. Nanostructured systems. Small-angle X-ray scattering/profiles. Drugs/delivery systems.

Neste trabalho, os sistemas nanoestruturados com diferentes níveis de organização foram obtidos através dos diagramas de fase ternários, utilizando tensoativos com de diferentes graus de lipofilicidade, o PPG-5-Ceteth-20 e o Oleth 10, e ácido oleico e miristato de isopropila como fases oleosas. Através dos diagramas foi possível observar diferenças significativas relacionadas com as características dos sistemas, devido à capacidade que o Oleth 10 (como tensoativo) e o ácido oleico (como fase oleosa) têm em diminuir a tensão interfacial, facilitando a formação de uma extensa região de sistemas transparentes. Através da microscopia de luz polarizada foi possível identificar as características isotrópicas e anisotrópicas dos sistemas, sendo posteriormente confirmadas pelas curvas de dispersão de raios X de pequeno ângulo (SAXS). Além disso, foi possível verificar que o aumento de água nas formulações proporcionou maior estruturação, permitindo a observação de picos mais estreitos e definidos nas curvas de SAXS.

Unitermos: Diagramas de fases ternários. Sistemas nanoestruturados. Curvas de dispersão de raios X de pequeno ângulo/perfis. Fármacos/sistemas de liberação.

INTRODUCTION

Important nanostructured systems are described by means of phase diagrams and used in the chemical and pharmaceutical industries for the development of drug delivery systems (Boonme *et al.*, 2006; Corrêa *et al.*, 2005). These systems can act as reservoirs controlling the

release rate of the drug, as well as the pharmacokinetic parameters, thus decreasing its toxicity and increasing its clinical efficacy. These characteristics enable these systems to maintain the therapeutic dose for an extended time, reducing the frequency of administration (Phan *et al.*, 2011; Tri-Hung *et al.*, 2011). A major problem associated with the development of such systems is related to the choice of excipients, which should be made carefully so as to meet certain requirements: the system should form readily and be stable, non-toxic, non-irritant and capable of solubilizing and incorporating the drug of interest (Trotta, 1999; Oliveira, 2004). The systems stabilized

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with nonionic surfactants are generally less affected by the presence of additives (buffer, electrolytes and preservatives) and changes in pH than those with ionic surfactants, and are safer and less likely to cause irritation (Kreilgaard, 2002; Garti *et al.*, 2004).

For years, microemulsions formed by long-chain nonionic surfactants have been studied as drug delivery systems. However, there are few studies on liquid crystal phases produced by these surfactants for this purpose (Wang *et al.*, 2006). In this study we used two nonionic surfactants, long chain polyoxyethylene (10) oleyl ether (Oleth 10) and polyoxypropylene, polyoxyethylene ether of cetyl alcohol (PPG-5-Ceteth-20), pharmacologically and toxicologically acceptable and capable of forming nanostructured systems (Ghosh *et al.*, 2011; Wang *et al.*, 2005; Bruschi *et al.*, 2008; El-Hadiry *et al.*, 2012). The oil component is also important, because it affects the structure of the system, which must be compatible with the drug used, especially if the latter is lipophilic (Podlogar *et al.*, 2005; Moreno, Ballesteros, Frutos, 2003). When these systems are applied to the skin, some fatty acids and esters can act as drug penetration enhancers, helping the percutaneous absorption of drugs that do not have good skin penetration (Agatonovic-Kustrin *et al.*, 2003; Valenta, Schultz, 2004). Unsaturated fatty acids are more effective in promoting percutaneous absorption of drugs than their saturated homologues (Garti, Arsenin, 1996). Therefore, for the preliminary preparation of phase diagrams, the fatty acid ester, isopropyl myristate, and monounsaturated fatty acid, oleic acid, were utilized.

MATERIAL AND METHODS

The main materials were: PPG-5-20-Ceteth (Procetyl®, CRODA, Brazil), Oleth 10 (Brij O® 10, Sigma - Aldrich, USA), oleic acid (Synth, Brazil), isopropyl myristate (Synth, Brazil) and ultrapure water (Milli-Q)

Ternary phase diagrams

The ternary phase diagrams were constructed in the form of an equilateral triangle, lines parallel to

each side representing concentrations of one of the components, at 10% intervals, up to 100% at the opposing vertex. Each point thus corresponds to a mixture of particular concentrations of surfactant, oil and water. The formulations were prepared by first mixing the components (w/w) at a temperature of $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$, stirred by a vortex mixer and then centrifuged. Formulations leading to homogeneous mixtures and those with evidence of phase separation were stored at room temperature for one week and analyzed. The components of the systems in the four phase diagrams are shown in Table I.

Physicochemical characterization of the formulations

With the aim of understanding the behavior of the surfactant molecules, while varying the type of oil and the amount of water, formulations within each of the four diagrams were analyzed, in which the content of oil was fixed at 10% and the surfactant and the water contents were varied (Table II).

Polarized light microscopy

A small number of formulations (F1-F12 in Table II) were placed between a cover slip and a glass slide and examined under polarized light. An Optical Leica Leitz DM RXE Microscope, equipped with a Moticam 2000 image capture system, was used to analyze various fields of each sample at room temperature. The isotropic or anisotropic behavior of each sample was observed. Photomicrographs were taken at 200 x magnification.

Small-angle X-ray scattering (SAXS)

The structural features of formulations listed in Table II were analyzed by SAXS measurements. Data were collected at the National Laboratory of Synchrotron Light (LNLS, Campinas, Brazil) at the SAXS1 beam line, equipped with a monochromator ($\lambda = 1.488\text{ }\text{\AA}$). An X-ray detector in a vertical position and a multichannel analyzer were used to capture the intensity of the SAXS

TABLE I - Compositions of the phase diagrams

Diagram	Surfactant	Phase Oil	Aqueous
D ₁	PPG - 5 - Ceteth - 20	Oleic acid	Water
D ₂	PPG - 5 - Ceteth - 20	Isopropyl myristate	Water
D ₃	Oleth 10	Oleic acid	Water
D ₄	Oleth 10	Isopropyl myristate	Water

TABLE II - Formulations in which the proportion of the oil is fixed at 10% and the ratio of surfactant / water is varied

D1	F1	F2	F3	D2	F4	F5	F6
PPG-5-Ceteth-20 %	80	70	60	PPG-5-Ceteth-20 %	80	70	60
Oleic acid %	10	10	10	Isopropyl myristate %	10	10	10
Water %	10	20	30	Water %	10	20	30
D3	F7	F8	F9	D4	F10	F11	F12
Oleth 10 %	80	70	60	Oleth 10 %	80	70	60
Oleic acid %	10	10	10	Isopropyl myristate %	10	10	10
Water %	10	20	30	Water %	10	20	30

measurements, $I(q)$, as a function of the scattering vector, q . Data were normalized with respect to the beam decay, detector sensitivity and sample transmission. The parasitic scattering intensity (of the cell window and air) was subtracted from the total scattering intensity. This setup allowed the scattering vector, q , to be varied between approximately 0.1 and 2.3 Å⁻¹.

RESULTS AND DISCUSSION

Ternary phase diagrams

The regions found in the phase diagrams were firstly divided, by a visual assessment of the corresponding formulations, into translucent and opaque systems. Subsequently, these regions were reclassified in terms of viscosity. This was done by observing the meniscus in a test tube containing the formulation, after inclining it at 90°. In this test, the fluid velocity along the wall of the tube is noted: low-viscosity formulations show fast and continuous flow, similar to that of propylene glycol, while intermediate-viscosity formulations exhibit slow flow along the tube, as a viscous liquid, and high-viscosity formulations show practically no flow along the tube, like a gel. The regions in the diagrams were thus classified as translucent low-viscosity systems (TLVS), translucent intermediate-viscosity systems (TIVS) and translucent high-viscosity systems (THVS). Systems with intermediate viscosity and a milky appearance were denominated intermediate-viscosity emulsion systems (IVES). Opaque systems with high-viscosity were classified as opaque high-viscosity systems (OHVS) and systems with phase separation as (PS).

The results show that the diagrams formed by PPG-5-Ceteth-20, regardless of the oil phase, showed homogeneous systems with very different levels of organization, over a wide range of combination of components. Figure 1 shows diagram D1 (PPG-5-Ceteth-20, oleic acid and water). The TLVS region was

obtained at a low water (10 to 20%), medium oil (10% to 50%) and high surfactant (80% to 40%) content. It was observed that when the water content was increased (20 to 40%) and the surfactant remained between 50 and 60%, the region of TLVS was converted to a more viscous region of organized systems (TIVS). At intermediate contents of the oil component (40 to 60%), when the surfactant was 30% and the water in small amounts, emulsion systems were formed. At high concentrations of water or oil phase, the low surfactant concentration promoted phase separation.

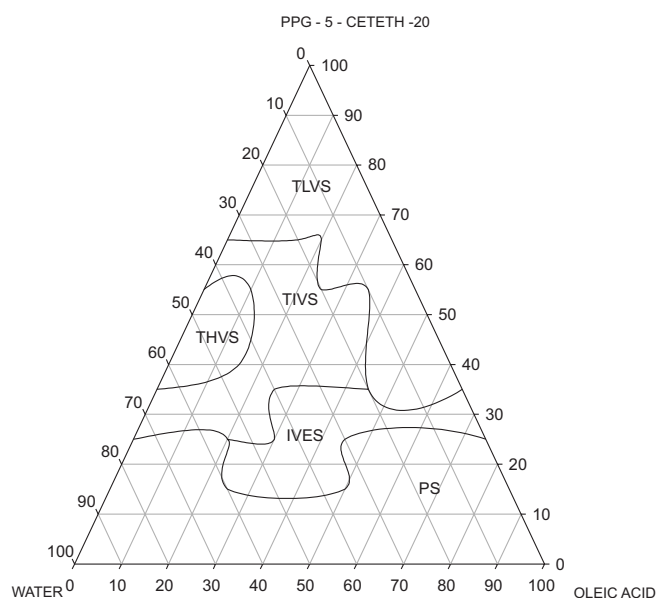


FIGURE 1 – Ternary phase diagram D₁ (PPG-5-Ceteth-20/Oleic acid/water): (TLVS) Translucent low-viscosity system; (TIVS) Translucent intermediate-viscosity system; (THVS) Translucent high-viscosity system; (IVES) Intermediate-viscosity emulsion system and (PS) Phase separation.

Figure 2 shows the diagram D2 (PPG-5-Ceteth-20, isopropyl myristate and water). In this diagram, some peculiarities were seen on increasing the volume of water. At concentrations about of 40% water, the formation of high-viscosity systems, mainly opaque (OHVS), was

observed. This contrasts with diagram D1, where the use of oleic acid facilitated the formation of a large region of TIVS and THVS, these systems showing organized structures and nanoscale sizes, reflected in their translucence. This effect was probably due to the oleic acid having the end group $-\text{COOH}$. Thus, it tends to act as a co-surfactant and cooperates in reducing interfacial tension, unlike isopropyl myristate, which has a nonpolar end group, $-\text{CH}_3$ (Wang *et al.*, 2006). The ability of surfactants to reduce the interfacial tension between oil and water allows translucent systems to form, based on structures smaller than a quarter of the wavelength of visible light, which do not scatter it (Garti, Aserin, 1996). The use of isopropyl myristate did not lead to the formation of emulsion systems. Phase separation again occurred at high concentrations of the oil and water or low concentrations of surfactant.

Other studies have also reported the potential of the components PPG-5-Ceteth-20/oleic acid and PPG-5-Ceteth-20/isopropyl myristate to form nanostructured systems. Those studies referred to the importance of increasing the water content to raise the level of organization and viscosity of these systems, an effect exploited particularly in the development of precursors of liquid crystalline phases for potential nasal administration of zidovudine and administration of propolis in periodontal pockets (Bruschi *et al.*, 2008; Carvalho *et al.*, 2010).

Diagrams D3 and D4 show that the surfactant Oleth 10, regardless of the oil used, also produced homogeneous

systems with very different levels of organization over a wide range of compositions. Figure 3 shows diagram D3 (Oleth 10, oleic acid and water). The TLVS region was obtained at low water (10 to 20%), medium oil (20 to 50%) and high surfactant (70 to 40%) concentrations. Differently from the diagrams obtained with PPG-5-Ceteth-20, Oleth 10 at high concentrations (between 80 and 70%) and low concentrations of water (10 to 20%) was able to form a larger TIVS region, this characteristic being related to the critical micellar concentration (CMC) of the surfactant, which is reached in these proportions, though it can be seen that the level of system organization still depended on increasing the water content (a feature that will be confirmed by SAXS curves). The combination of surfactant at intermediate concentrations (around 30%) and the oily component between 40 and 60% favored the formation of emulsion systems. Phase separation occurred at low concentrations of surfactant.

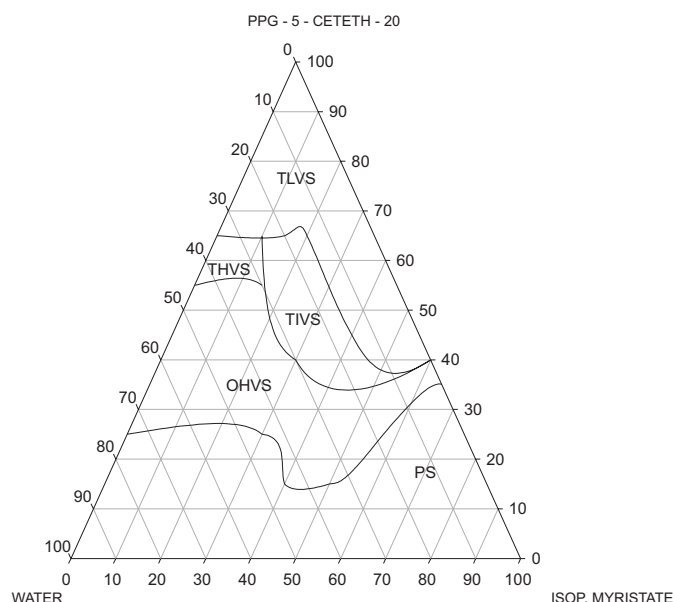


FIGURE 2 – Ternary phase diagram D₂ (PPG-5-Ceteth-20/isopropyl myristate/water): (TLVS) Translucent low-viscosity system; (TIVS) Translucent intermediate-viscosity system; (THVS) Translucent high-viscosity system; (OHVS) Opaque high-viscosity systems and (PS) Phase separation.

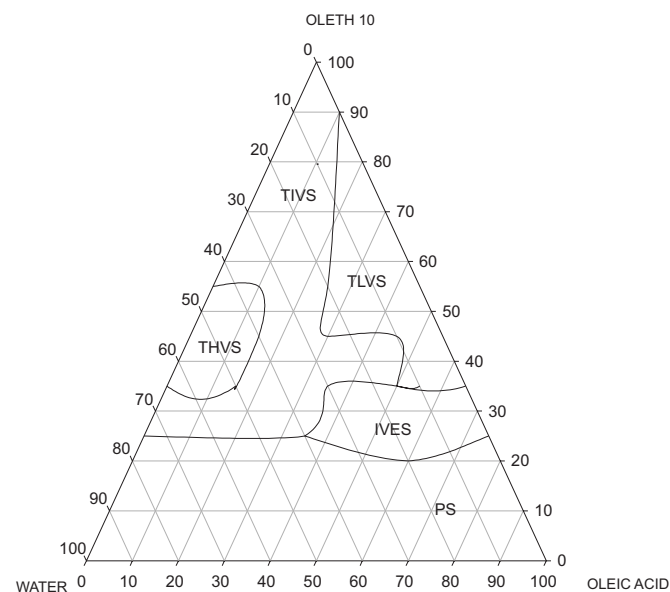


FIGURE 3 – Ternary phase diagram D₃ (Oleth 10/oleic acid/water): (TLVS) Translucent low-viscosity system; (TIVS) Translucent intermediate-viscosity system; (THVS) Translucent high-viscosity system; (IVES) Intermediate-viscosity emulsion system and (PS) Phase separation.

Figure 4 shows diagram D4 (Oleth 10, isopropyl myristate and water). In contrast to PPG-5-Ceteth-20, Oleth 10 led to the formation of an extended region of translucent and organized structures. This difference may be due to Oleth 10 possessing fewer ethylene oxide units than PPG-5-Ceteth-20, which represents a smaller amount of oxygen in the Oleth 10 molecule, thus reducing the number of possible hydrogen bonds with the water present in the formulation. Thus, surfactants with a higher

degree of ethoxylation show a lower capacity to reduce the interfacial tension, because the bonding between the oxygen atoms of the surfactant and the hydrogen of water hinder their mobility toward the surface of oil droplets, providing less translucent systems (Neto *et al.*, 2009). The region of TLVS was again obtained at low water (10 to 20%), medium oil (20 to 50%) and high surfactant (70 to 40%) concentrations. Diagram D4 features a small region of high-viscosity opaque systems (OHVS), at concentrations of water above 40%. By comparison with the other three diagrams, it appears that oleic acid extended the TIVS region. The formation of emulsion systems was seen at intermediate concentrations of the oil component (40 to 60%). Phase separation again occurred at low concentrations of surfactant.

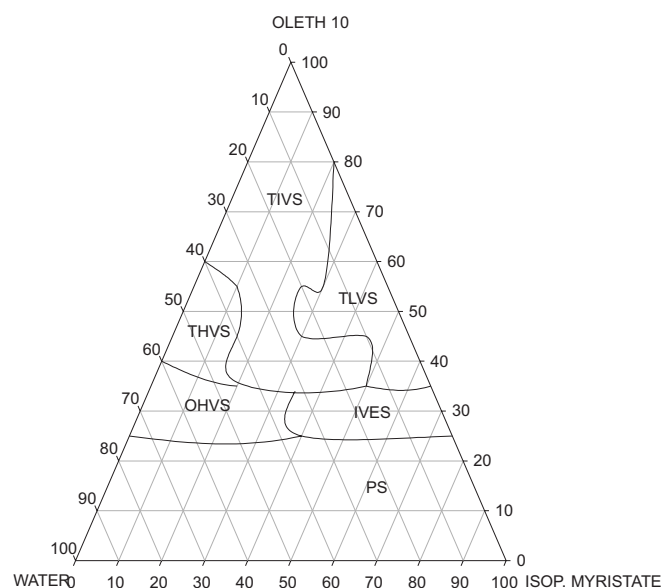


FIGURE 4 – Ternary phase diagram D₄ (Oleth 10/isopropyl myristate/water): (TLVS) Translucent low-viscosity system; (TIVS) Translucent intermediate-viscosity system; (THVS) Translucent high-viscosity system; (OHVS) Opaque high-viscosity systems; (IVES) Intermediate-viscosity emulsion system and (PS) Phase separation.

Some other studies have also investigated the formation of nanostructured systems by mixtures of Oleth 10 with the oil phases: isopropyl myristate and oleic acid. These studies assessed in detail the nanostructures obtained, by means of rheological and SAXS analyses (Wang *et al.*, 2005; Wang *et al.*, 2006). However, they did not investigate the changes that occur in these systems as the water content is increased, or the effects of using surfactants with varying degrees of ethoxylation, a characteristic described earlier that interferes directly in the structure of these systems and, consequently, in the

diffusion and release of drugs incorporated in them.

Physicochemical characterization of the formulations

Polarized light microscopy

Figures 5 to 7 show photomicrographs of formulations, which have a fixed proportion of the oil (10%), but varying amounts of surfactant and water. The composition of each formulation is shown in Table II. The formulations containing 80 to 70% surfactant and 10 to 20% water (F1, F2 of diagram D1 and F4 and F5 of diagram D2) showed isotropic behavior (dark field), as in Figure 5, where the sample has only one refractive index in all directions, suggesting the formation of microemulsion systems. In diagram D1, as the concentration of water was raised to 30% and the surfactant fell to 60% (F3), the system became anisotropic, causing a deviation in the plane of polarized light (birefringence), revealed by the appearance of “maltese crosses” in the micrograph, which characterize a lamellar liquid crystalline phase (Figure 6). On the other hand, when the water was increased to 30% (F6) in diagram D2, there was a structural change in the system, making it more ordered and viscous, so that the anisotropy of the sample showed a hexagonal liquid crystal phase (Figure 7).



FIGURE 5 – Representative photomicrograph of the formulation containing 80-70% surfactant, 10-20% water and 10% oil, present in diagram (D1 and D2). Magnified 20 X.

The formulations containing Oleth 10 (diagrams D3 and D4) at a high surfactant concentration (80%) and low water (10%) (F7 and F10) also caused a deviation in the plane of polarized light, resulting in the appearance of maltese crosses, as seen in Figure 6. Samples of F8 and F9 of the oleic acid diagram (D3) and F11 and F12 of the isopropyl myristate diagram (D4) also anisotropic behavior of the lamellar phase (maltese crosses).

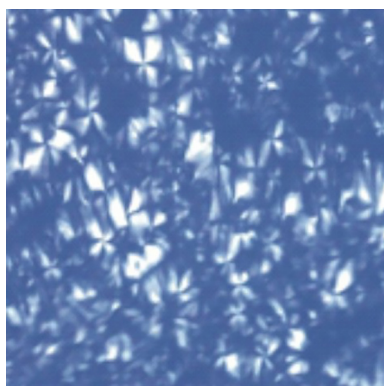


FIGURE 6 – Representative photomicrograph of the formulation containing 60% surfactant, 30% water and 10% oil, present in diagram (D1). Magnified 20 X.

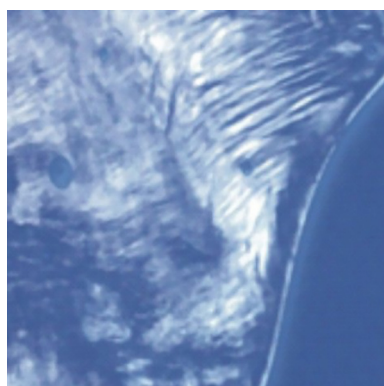


FIGURE 7 – Representative photomicrograph of the formulation containing 60% surfactant, 30% water and 10% oil, present in diagram (D2). Magnified 20 X.

Small-angle X-ray scattering (SAXS)

Figures 8-11 show the curves of scattering intensity $I(q)$ as a function of the scattering vector (q). In the SAXS curves of formulations F1, F2, F4 and F5 (diagrams D1 and D2), there was a broad peak characteristic of microemulsions (Beaucage *et al.*, 1995). For formulation F3 (diagram D1), the increase in water content to 30% and decrease in the surfactant to 60% led to a great shift in the position (q_{max}) of the peak intensity to lower q , indicating a greater distance between the scattering objects. It is possible to calculate this distance from the peak position (q_{max}), as $d = 2\pi / q_{max}$. A second peak can be seen at double the q of the first. The ratio between the two distances, $d_1/d_2 = 2$ demonstrates a periodicity equivalent to a lamellar liquid crystalline phase, confirmed by the presence of “maltese crosses” in the polarized light micrograph. Formulation F6 (diagram D2), with the same increase in water content (30%), showed a smaller distance between

the scattering objects (more highly organized system) and the ratios $d_1/d_2 = 1.73$ and $d_1/d_3 = 2$, a periodicity specific to a hexagonal liquid crystalline phase, which caused the streaks seen under polarized light microscopy in Figure 7.

The formulations with high concentrations of Oleth 10 (80 to 70%) and low water concentrations (10 to 20%) (F7, F8, F10 and F11), produced SAXS curves with periodicity specifying a lamellar liquid crystalline phase. This effect on the organization of the formulations caused by high concentrations of this surfactant, in contrast to PPG-5-Ceteth-20, probably depends on its CMC, which enables the formation of micellar aggregates that are organized into ordered structures, with definite peaks. Formulations F9 and F12 also showed definite peaks and, by the ratio $d_1/d_2 = 2$, showed a lamellar phase.

The SAXS analysis, besides identifying the nanostructures, also provides further information on the levels of organization of liquid crystalline arrangements. In the SAXS curves, it was observed that the peaks became narrower in formulations in which the proportion of water was raised. Thus, the increase in water afforded the thickening of the structure in these systems. This effect is probably related to the hydrophobic portion of the surfactant, which protects itself from the extra water, thus increasing its level of packaging. This consequently makes the distance between the scattering objects wider, providing narrower and well-defined peaks.

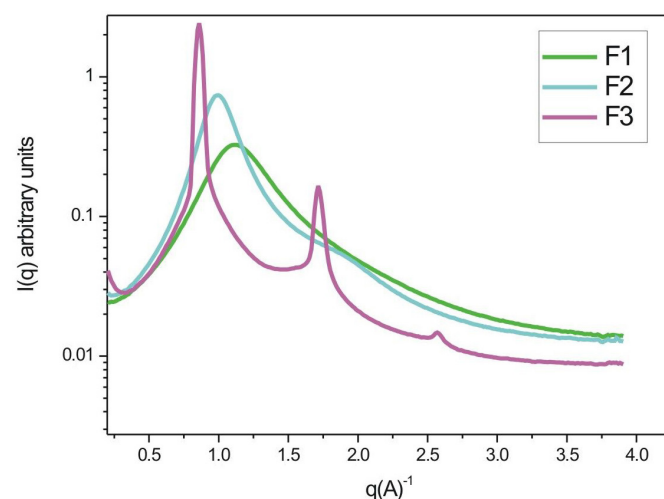


FIGURE 8 – SAXS profiles of systems stabilized by 80, 70 and 60% (PPG-5-Ceteth-20); 10, 20 and 30% (water) and 10% (oleic acid).

According to Drummond and Fong (2000), the release profile from a nanostructured system is influenced by characteristics of the drug, such as diffusion, solubility and partition coefficient, and physicochemical properties

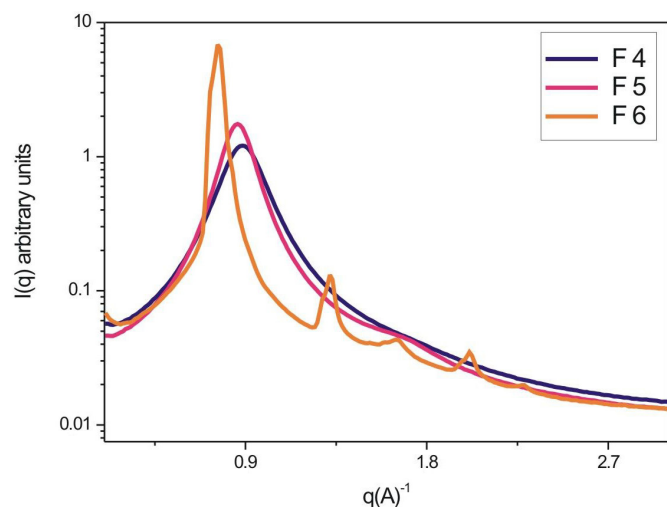


FIGURE 9 – SAXS profiles of systems stabilized by 80, 70 and 60% (PPG-5-Ceteth-20); 10, 20 and 30% (water) and 10% (isopropyl myristate).

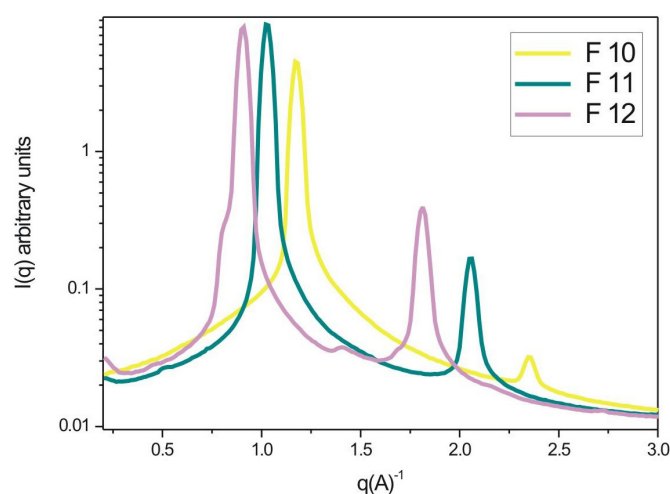


FIGURE 11 – SAXS profiles of systems stabilized by 80, 70 and 60% (Oleth 10); 10, 20 and 30% (water) and 10% (isopropyl myristate).

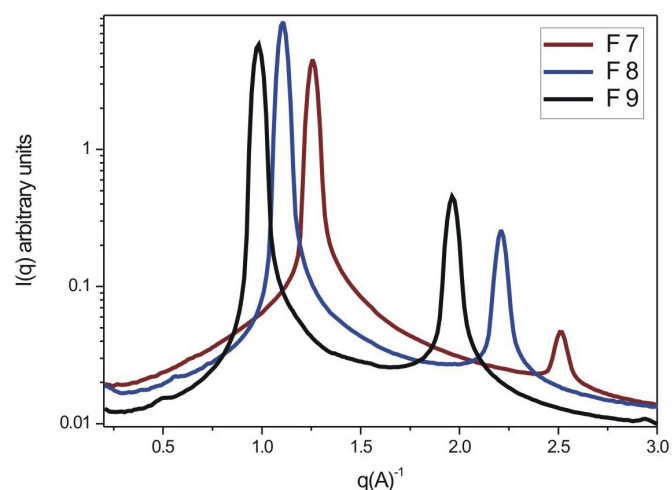


FIGURE 10 – SAXS profiles of systems stabilized by 80, 70 and 60% (Oleth 10); 10, 20 and 30% (water) and 10% (oleic acid).

of the system, such as the nature and proportion of the components. Thus, Brinon *et al.* (1998) studied a study about the influence of surfactants with differing degrees of lipophilicity on the diffusion and permeation of substances carried in liquid crystal systems. Specifically, they reported the effects of distinct liquid crystal arrangements on the diffusion and permeation of two compounds used as sunscreens, benzophenone-4 and 2-ethylhexyl methoxycinnamate, which have quite distinct solubility properties. They found that the systems formed by a lipophilic surfactant allowed faster diffusion of the lipid sunscreen (2-ethylhexyl methoxycinnamate) while the hydrophilic surfactant promoted faster diffusion of the hydrophilic sunscreen (benzophenone-4).

The entire set of results obtained in our study, from the creation of nanostructured systems until the structural characterization revealed the importance of the various components of the diagrams, as the concentration of each. By researching the organization levels of nanostructured systems, it is possible establishing parameters to understand the complex relationship between the composition and structure of these systems, with the diffusion and release of different kind of drugs.

CONCLUSION

In this study, ternary phase diagrams displayed several homogeneous systems with different organizational levels, a characteristic responsible for modulating the diffusion and delivery of drugs. In diagrams D3 and D4, a larger region of translucent and organized structures was observed than in diagrams D1 and D2. This difference was probably due to the surfactant Oleth 10 having a greater capacity than PPG-5-Ceteth-20 to reduce the interfacial tension between water and oil. Oleic acid, the oil in diagrams D1 and D3, possibly served as a co-surfactant, cooperating in reducing interfacial tension and thus enlarging the translucent systems region. By polarized light microscopy, isotropic and anisotropic behavior could be seen which was later confirmed by SAXS analysis, enabling a better understanding of the organization levels of these systems. The results obtained above will contribute to the design of nanostructured carrier systems for drugs with distinct physicochemical properties. Thus, with knowledge of the composition and levels of organization of the systems, it will be possible to modulate

the process of diffusion and release of these drugs.

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